Kinetics of cyclization of *N*-substituted 1-(2-nitrophenyl)-guanidines and mechanism of the cyclization reactions

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Dedicated to Professor P. Hrnčiar, DrSc., in honour of his 60th birthday

Kinetic measurements of cyclization of 3-ethyl-1-(2-nitrophenyl)-guanidine and 2-phenyl-1-(2-nitrophenyl)guanidine to 3-ethyl- and 3-phenylamino-1,2,4-benzotriazine 1-oxide were carried out in dependence on pH of the reaction medium by spectrophotometry.

The rate constants k_I calculated for the unimolecular order of the reaction were proved to be linearly dependent on pH of the medium. Also the rate constants k_{II} for the bimolecular order of the reaction were calculated.

From the results of this kinetic study and the published experimental findings about the properties of 2-nitrophenylguanidines and their cyclization to substituted 3-amino-1,2,4-benzotriazine 1-oxides the mechanism of this base-catalyzed reaction was proposed.

Спектрофотометрически изучена зависимость скорости циклизации 3-этил-1-(2-нитрофенил)гуанидина и 2-фенил-1-(2-нитрофенил)гуанидина в 3-этил- и 3-фениламино-1,2,4-бензотриазин-1-оксид от pH реакционной среды.

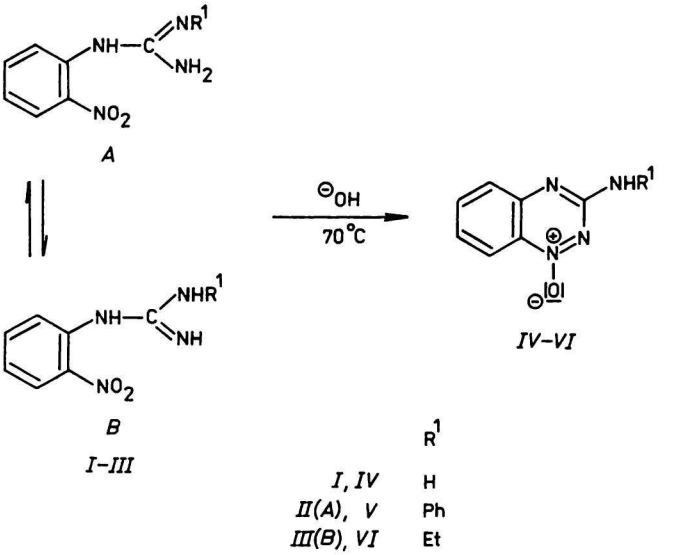
Показано, что константы скорости k_I, рассчитанные для псевдомономолекулярного протекания циклизации, находятся в линейной зависимости от pH реакционной среды. Были также рассчитаны значения констант скорости k_{II} для бимолекулярного процесса.

На основании результатов кинетического исследования и других ранее публикованных экспериментальных данных о свойствах 2-нитрофенилгуанидинов и их циклизации в замещенные 3-амино-1,2,4-бензотриазин-1-оксиды предлагается механизм этой циклизации, катализируемой основаниями.

In order to be able to study the cyclization reaction between the nitro and the guanidine groups under formation of 1,2,4-benzotriazine 1-oxide ring that was at first described by *Arndt* [1], we prepared some of the 4-substituted 2-nitrophenylguanidines [2], variously *N*-substituted 2-nitrophenylguanidines [3] and studied their acid-base properties [3, 4] and their cyclization reactions under base catalysis [5, 6].

The aim of this work was on the one hand the kinetic study of the cyclization of 2-phenyl-1-(2-nitrophenyl)guanidine (*II*) and 3-ethyl-1-(2-nitrophenyl)-

guanidine (*III*) to the corresponding 1,2,4-benzotriazine 1-oxides *V* and *VI* in the dependence on pH of the reaction medium (Scheme 1) and on the other hand using these results in connection with the experimental findings from works [3—6] to propose the most probable general mechanism of the cyclization reaction of *N*-substituted 1-(2-nitrophenyl)guanidines.



Scheme 1

The experimental results of these kinetic measurements are similar to the results obtained during the cyclization of 4-substituted 2-nitrophenylguanidines [6]. It means that again the validity of the kinetic equation derived on the basis of the proposed general reaction scheme was confirmed and that the logarithm of the rate constant k_I calculated for the unimolecular order of the reaction is linearly dependent on pH with the slope very close to the value of 1 (Table 1). This result shows that also the cyclization of both studied compounds is of the first order in respect to the concentration of hydroxide ions. The validity of the relation derived in [6] for the whole reaction order equal to 2 was also confirmed.

From the rate constants k_I obtained (Tables 2 and 3), from the measured values of pH and from the ionic product of water at the temperature of the reaction [7] the values of the rate constants k_{II} were calculated.

The comparison of the rate constants k_{II} of cyclization of compounds *II* and

Table 1

The dependence of the rate constant k_I(comp) on pH

Compound	n	$\log k_{II}$(comp)	r
II	0.976	−3.317	0.999
III	1.003	−3.051	0.999

$k_I(\text{comp}) = k_{II}(\text{comp}) \cdot [OH^-]^n$

$\log k_I(\text{comp}) = n(\log K_w^{70} + \text{pH}) + \log k_{II}(\text{comp})$

where n, r, K_w^{70} are order of the reaction, correlation coefficient, autoprotolysis constant of water at 70 °C.

Table 2

Rate constants $k_I(II)/s^{-1}$ and $k_{II}(II)/(dm^3\ mol^{-1}\ s^{-1})$ calculated from the experimental data of the cyclization of compound *II* to *V* in dependence on pH at the temperature of 70 °C

pH	$k_I(II)$	$-\log k_I(II)$	$-\log k_{II}(II)$
9.71	$(5.888 \pm 0.080) \times 10^{-7}$	6.230	3.262
9.92	$(9.705 \pm 0.095) \times 10^{-7}$	6.013	3.255
10.05	$(1.412 \pm 0.017) \times 10^{-6}$	5.850	3.222
10.16	$(1.811 \pm 0.042) \times 10^{-6}$	5.742	3.224
10.28	$(2.104 \pm 0.079) \times 10^{-6}$	5.677	3.279
10.70	$(5.470 \pm 0.164) \times 10^{-6}$	5.262	3.284
10.95	$(9.772 \pm 0.312) \times 10^{-6}$	5.010	3.282
11.07	$(1.343 \pm 0.032) \times 10^{-5}$	4.871	3.263
11.18	$(1.664 \pm 0.051) \times 10^{-5}$	4.779	3.281
			3.261 ± 0.023

Table 3

Rate constants $k_I(III)/s^{-1}$ and $k_{II}(III)/(dm^3\ mol^{-1}\ s^{-1})$ calculated from the experimental data of the cyclization of compound *III* to *VI* in dependence on pH at the temperature of 70 °C

pH	$k_I(III)$	$-\log k_I(III)$	$-\log k_{II}(III)$
9.59	$(6.982 \pm 0.173) \times 10^{-7}$	6.156	3.068
9.78	$(1.045 \pm 0.011) \times 10^{-6}$	5.981	3.083
9.89	$(1.469 \pm 0.024) \times 10^{-6}$	5.833	3.045
10.03	$(2.061 \pm 0.050) \times 10^{-6}$	5.686	3.038
10.18	$(2.661 \pm 0.063) \times 10^{-6}$	5.575	3.077
10.31	$(3.819 \pm 0.091) \times 10^{-6}$	5.418	3.050
10.69	$(9.333 \pm 0.302) \times 10^{-6}$	5.030	3.042
10.98	$(1.762 \pm 0.039) \times 10^{-5}$	4.754	3.056
11.16	$(2.576 \pm 0.071) \times 10^{-5}$	4.589	3.071
			3.059 ± 0.017

III (Tables 2 and 3) with the value of k_{II} of unsubstituted 2-nitrophenylguanidine (*I*) ($\log k_{II} = -2.776 \pm 0.021$) led to the following relation

$$k_{II}(I) > k_{II}(III) > k_{II}(II)$$

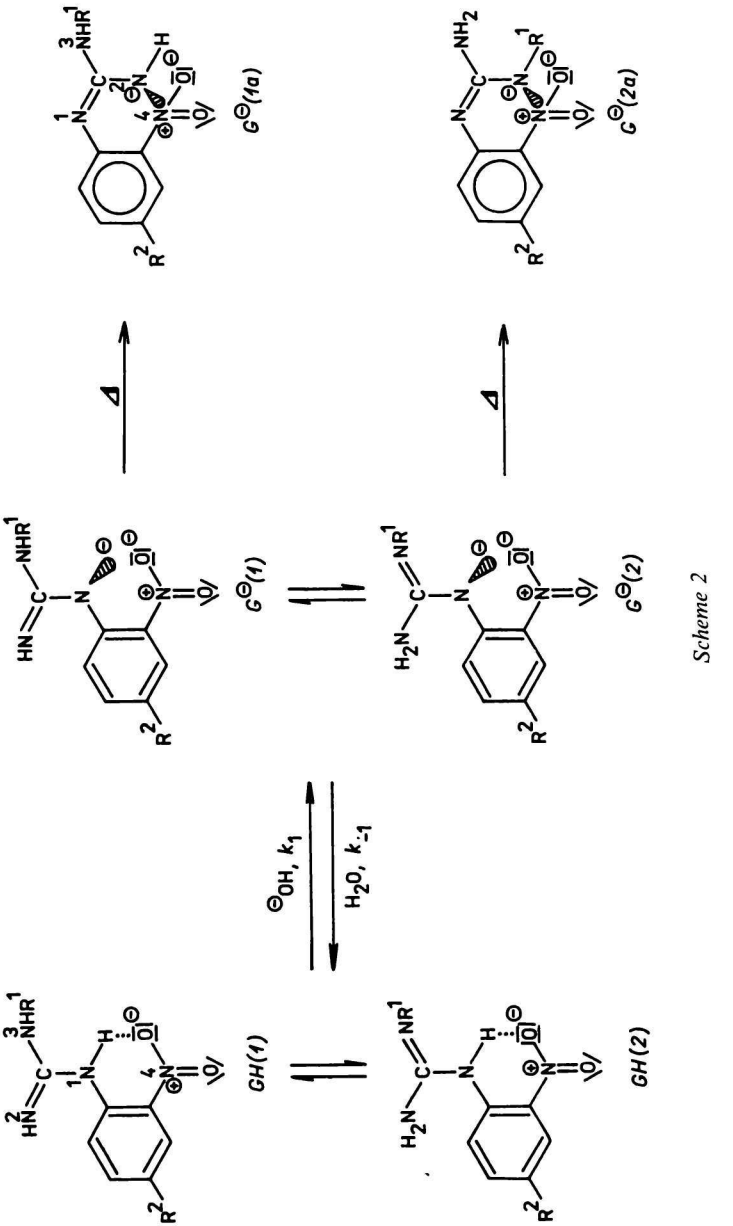
One should take into account the fact that unsubstituted 2-nitrophenylguanidine (*I*) in contrast to compounds *II* and *III* has for the attack of the nitrogen atom of the nitro group two equivalent nitrogen atoms (*cf.* the conclusions from [4]) and the rate of its cyclization for the statistic reasons should be double. This leads to the changed order of magnitudes of the rate constants in the relation

$$k_{II}(III) > 1/2k_{II}(I) > k_{II}(II)$$

The order of the rate constants corresponds now with the electronic effect of the substituents bound at the attacking nitrogen in anion of 2-nitrophenylguanidine system formed from compounds *I*, *II*, and *III*.

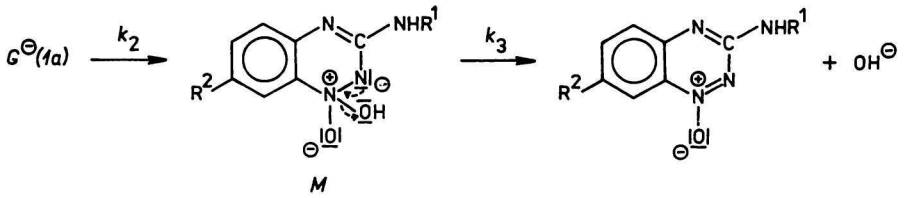
Our proposal of the reaction mechanism is based on the knowledge formerly obtained. Thus, IR spectra of 4-substituted 2-nitrophenylguanidines [3, 4] as well as the electrochemical study [8] show that these compounds are in a conformation in which there is a hydrogen bond between the hydrogen atom bound at the nitrogen atom N(1) of the guanidine group and the oxygen atom of the nitro group. Because the hydrogen bond is situated in the plane of the 2-nitrophenyl system, the lone electron pair located at the nitrogen N(1) is conjugated with the guanidine group and partially also with 2-nitrophenyl (Scheme 2). The previous knowledge [3, 4] shows that 4-substituted 2--nitrophenylguanidines and compound *III* are present in the tautomeric form *GH(1)*, compound *II* in the form *GH(2)*.

The reaction of cyclization is started by the proton elimination from the nitrogen atom N(1) of the guanidine group. The agent is the present catalyst — hydroxide anion. The anion $G^{\ominus}(1)$ or $G^{\ominus}(2)$ (Scheme 2) so formed is stabilized by the delocalization of the negative charge being at N(1) on both the 2-nitrophenyl system and the guanidine part of the molecule. The conformation of the anion after extinction of the hydrogen bond is changed due to repulsion of the negative charge at N(1) and the negative charge at the oxygen atom of the nitro group. The higher temperature makes the rate of rotation around the bond C_{arom}—N(1) quicker. Thus, the rotation of the guanidine group proceeds causing discarding of the conjugation with 2-nitrophenyl. But during this process one of the two nitrogen atoms N(2) or N(3) gets into bonding distance to the nitrogen atom N(4) (Scheme 2) under gentle rotation of the nitro group out of the benzene ring plane (the molecule modelling shows the angle of about 30°). The rotation of the guanidine group out of the conjugation with 2-nitrophenyl causes an increase in the electron density at the atoms N(2) and



Scheme 2

N(3), respectively. In case the substituent $R^1 = H$ the structure $G^{\ominus}(1a)$ is identical with the structure $G^{\ominus}(2a)$ and the whole molecule is in a very suitable arrangement for the bond formation between the atoms N(2)—N(4) (Scheme 3).



Scheme 3

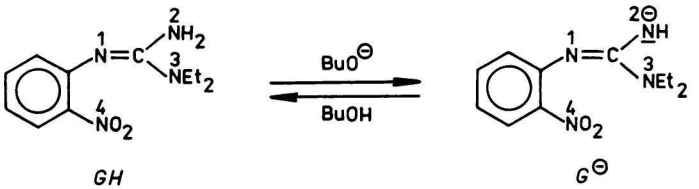
The following cyclic intermediate is characterized on the one hand by the interaction N(2)—N(4) and on the other hand by the interaction of the hydrogen atom bound at N(2) with the oxygen atom of the nitro group forming the intermediate *M* [6] (Scheme 3). The measured rate constants of the cyclization show a significant influence of the substituent R^2 in position 4 of the benzene ring on this reaction step. In case R^1 is phenyl or ethyl group (cyclization of compounds *II* and *III*) the arrangement of molecule $G^{\ominus}(2a)$ (Scheme 2) is unfavourable for a ring closure because of the steric repulsion between the oxygen atoms of the nitro group and the substituent R^1. Any migration of the substituent R^1 at the oxygen atom of the nitro group is improbable. Therefore, during the cyclization of compounds *II* and *III* the molecules occupy energetically more advantageous conformation (better conjugated) described by the structure $G^{\ominus}(1a)$ and the reaction proceeds *via* the transition state mentioned before giving rise to the intermediate *M*.

In the following reaction step under hydroxide ion (catalyst of the reaction) splitting off supported by the aromatization of the system the corresponding derivative of 3-amino-1,2,4-benzotriazine 1-oxide is formed (Scheme 3).

The unwillingness of 1,3-diethyl- and 1,1,3-triethyl-2-(2-nitrophenyl)guanidines to enter into the reaction of cyclization (we were not able to cyclize these compounds [5]) could be explained partly by an inappropriate arrangement of the $G^{\ominus}(2a)$ anion (Scheme 2) characterized by the already mentioned steric repulsion between R^1 and the oxygen atoms of the nitro group, partly by a very low probability of the migration of the ethyl group.

The cyclization of 1,1-diethyl-2-(2-nitrophenyl)guanidine could be carried out only by the treatment with a strong base in an anhydrous medium (butoxide anion) [5]. Its pathway is described by the following succession of steps. The

compound is in the tautomeric form *GH* (Scheme 4) with the double bond situated between the nitrogen atom N(1) and the carbon atom of the guanidine group [3].



Scheme 4

The cyclization is here obviously started by the proton elimination from the primary amino group by the action of the used base. A stabilization of the negatively charged anion $G^{\ominus}$ by the delocalization on the guanidine group is limited due to cross-conjugation of 2-nitrophenyl with the diethylamino group. Anion $G^{\ominus}$ can therefore change into a more stable molecule in three ways, as it was observed. It can be either by protonation forming again the starting compound (Scheme 4) or by the decomposition to 2-nitroaniline or finally by the cyclization (both at higher temperature). The supply of energy causes the change of the conformation of anion $G^{\ominus}$ by the rotation around the bond C_{arom}—N(1) and disturbs the conjugation of the guanidine group with 2--nitrophenyl.

The following steps of the reaction mechanism are like in the formerly mentioned cases of cyclization, *i.e.* the hydroxide anion splitting off and finally the system aromatization.

Experimental

The spectrophotometric measurements were carried out on the instrument Unicam SP 1800 with the thermostated cell compartment SP 874. pH was measured on a pH-meter Radelkis OP-208 with the combined glass electrode OP-8083. For calibration the set of standard buffer solutions (Institute of Sera and Vaccines, Prague) and the saturated calcium hydroxide aqueous solution at the temperature of 25 °C (pH = 12.454) [9] were used. The conditions of spectrophotometric measurements and working up of the kinetic data were performed according to [6]. The synthesis of compounds *II* and *III* and their identification is given in [3]. UV VIS characteristics of the compounds *V* and *VI* are listed in Table 4. Kinetic measurements were carried out at the wavelength of the maximum absorption of products *V* and *VI* in the longwave region. The results of the kinetic measurements are presented in Tables 2 and 3.

Table 4

Values of the molar absorptivity coefficient ε and wavelength λ_{max} in the spectra of compounds *V* and *VI* measured in water

Compound	λ_{max}/nm ($\varepsilon \cdot 10^{-3}$/(m^2 mol^{-1}))			
V	216 (2.143)	244 (2.375)	262 (2.121)	434 (0.331)
VI	224 (1.132)	—	276 (2.753)	450 (0.294)

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